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REVIEW

Engineered nanostructures: A review of their synthesis, characterization and toxic hazard considerations

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Abstract Research work on the synthesis, designing and characterization of nanostructures has been extensively documented in the last decades. This in-depth documentation not only enabled researchers to understand the relationship between the nanostructure properties, size, shape, and composition but also have given them immense control over their manufacturing. This enhanced knowledge, cemented the switching of academic nanotechnology research into industrial products. However; despite the recent accomplishment in synthesis, characterization and application of the nanostructure materials, a complete knowledge/information of their interactions with biological systems is still not available. Hence, it is difficult to forecast the injurious biological responses of these novel nanostructures to humans, animals, insects and plants. Due to this hesitancy, safety regulatory authorities and general public have raised their concerns to the manufacturing and use of nanostructure-based products. Consequently, it is vital for the researchers to concentrate more on safe designing, manufacturing and characterization of nanostructures before these could meet human and communal needs. This review is taking an overview of the increasing investments in nanotechnology, designing, synthesis and characterization of nanostructures and their in vitro and in vivo toxicities.

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Contents

1. Introduction

In the past decades, extensive research has been carried out and documented on the synthesis and characterization of nanoscale materials, which has not only enabled researchers to have an in-depth knowledge of the relationship between the properties, size, shape, and composition, but also immense control over the manufacturing of materials ranging from 1 to 100 nm etc. Early investment in nanotechnology research with serious intentions begun in the period of 1997–2002 (Table 1), which rose to 8.6 billion US$ in 2004 (Medintz et al., 2005; Caruthers et al., 2007) and by 2007 more than 300 nanostructure based products (Fig. 1a), that accounted for 147 billion US$, were available in the market (Project on Emerging Nanotechnologies Consumer Products Inventory, 2008). By 2012, the increase in investment is forecasted to reach 1 trillion US$. An array of engineered nanostructures (Fig. 1b) such as carbon nanotubes (CNTs), fullerene and fullerene derivatives, polymer electrospun nanofibers membranes, zinc oxide (ZnO) nanofibers, gold (Au), silver (Ag), iron oxide (Fe_3O_4), titanium oxide (TiO_2), silicon oxide (SiO_2, quantum dots (QDs), etc., were produced. Beside this novel processes such as discharge method, chemical vapor deposition (CVD) and laser ablation (CNTs), electrospinning (polymer and metal oxide nanofibers), microemulsions (Pileni et al., 1993), and polymeric coatings (Au-nanoparticles (NPs)) (Suslick et al., 1996), chemical reduction (Leopold and Lendl, 2003; Caswell et al., 2003; Pillai and Kamat, 2004; Yin et al., 2002; Zhu et al., 2004; Chaki et al., 2004; Sun et al., 2003; Sun and Xia, 2002; Chen and Huang, 2002; Wang et al., 2005), template method (Faure et al., 2003; Chen and Carroll, 2002; Mandal et al., 2003; Malandrino et al., 2004; Behrens et al., 2004; Morley et al., 2002), electrochemical and/or ultrasonic-assisted reduction (Johans et al., 2002; Zhang et al., 2002; Ma et al., 2004; Yin et al., 2003; Cheng and Yao, 2005), photo-induced reduction (Socol et al., 2002; Shchukin et al., 2003; Zhang et al., 2003a; Junior et al., 2003; Jin et al., 2003; Mallick et al., 2004; Kryukov et al., 2003; Cozzoli et al., 2004), microwave-assisted synthesis (Liu et al., 2004; Yamamoto et al., 2004; Komarneni et al., 2002; Yin et al., 2004; Qin et al., 2002; Hornebecq et al., 2003), irradiation reduction (Choi et al., 2003; Xin et al., 2004; Tsuji et al., 2003; Zheng et al., 2004), micro-emulsion (Zheng et al., 2003; Zhang et al., 2003b; Maillard et al., 2003; Maillard et al., 2002; McLeod et al., 2003; Egorova and Revina, 2002; Naik et al., 2002), biochemical reduction (Gardea-Torresdey et al., 2003; Shankar et al., 2003; Kowshik et al., 2003; Ahmad et al., 2003; Bhainsa and DSouza, 2006; Shankar et al., 2004) (Ag-NPs), solution precipitation (Fe_3O_4-NPs) (Omer et al., 2011), hydrolysis and calcinations, reactor flame and furnace synthesis (Jang, 2001), sol–gel method (TiO_2 NPs) (Jiu et al., 2007), hydrolysis and condensation of tetraethylorthosilicate (TEOS) (Corradi et al., 2006), and two-stage hydrolysis in aqueous medium (SiO_2-NPs) (Guo et al., 2008), were also developed, which opened a new world of innovative possibilities. These novel materials and methods are anticipated to have a substantial impact on a variety of sectors i.e. energy (e.g., solar cells, fuel cell and energy storage devices, etc.), electronics (e.g., light emitting diodes, silicon chips, etc.), aerospace (e.g., light weight superior strength materials, radar absorbing coatings, jet and rocket fuel, etc.) and medicine (e.g., diagnostic imaging, photodynamic therapy (PDT) agents, actuators, gene and drug delivery devices, photothermal treatment triggers, etc.).

Table 1 Global research and development spending (US $ in millions) (Borm et al., 2006).

Country/region	1997	2002
USA	432	604
Western Europe	126	350–400
Japan	120	750
South Korea	0	100 pa (for 10 yrs)
Taiwan	0	70
Australia	0	40
China	0	40
Rest of World	0	270

As the transition of these novel nanostructures from academic research findings to industrial products (Maynard et al., 2006; Tsuji et al., 2006) accelerated (according to a report of Royal Society and Royal Academy of Engineering, the production of nanomaterials for use in structural, sink care products and environmental applications will increase in the range of 10–10^5 tons/year (Table 2) (Royal Society and Royal Academy of Engineering, 2004)), the potential direct and indirect threats posed by these products to environment and human health have begun to surface (Tsuji et al., 2006; Raviraja and Kandikere, 2007). At present an inclusive knowledge of the interactions of nanostructures with biological systems is not available (John, 2007). Therefore it is foggy to predict the harmful biological responses of these novel nanostructures to humans, animals, insects and plants (Colvin, 2003). Hence, it is obligatory for researchers to concentrate more on gaining inclusive knowledge of the size, shape, composition, and aggregation dependent interactions of nanostructures with biological system; which would lead to human and

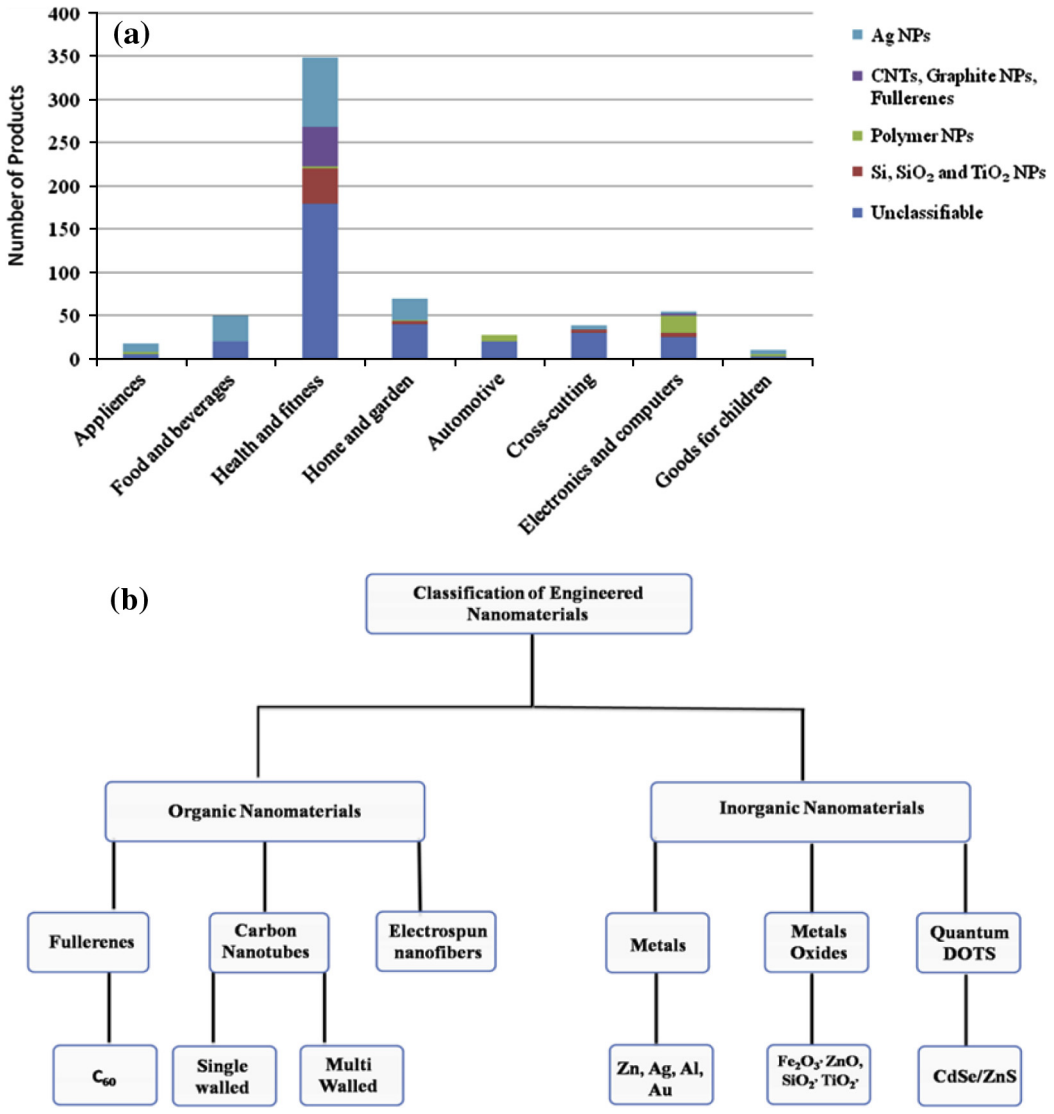

Figure 1 Summary of nanostructures; (a) products and application area (Hansen et al., 2008; Hristozov and Malsch 2009) and (b) classification.

communal safety (Royal Society and Royal Academy of Engineering, 2004).

1.1. Nanostructures and their synthesis

The synthesis of nanostructures is as versatile as the materials themselves e.g., fullerenes, which is an allotrope form of carbon (exist as hollow spheres (buckyballs), ellipsoids (closed quadric surface), and nanotubes (single-walled carbon nanotubes (SWCNTs) and Multi-walled carbon nanotubes (MWCNTs)) occur naturally as combustion products. Synthetically fullerenes are fabricated by vaporization of graphite *via* resistive heating (Krätschmer et al., 1990), combustion of simple hydrocarbons in fuel-rich flames (Howard et al., 2001) and UV laser irradiation of geodesic polyarenes (Scott et al., 2002; Scott, 2004). Momentous synthetic challenges are yet to be overcome to prepare higher order fullerenes and their derivatives e.g., ^{13}C-labeled fullerenes, heterofullerenes, azafullerenes, etc. CNTs were prepared in 1991 *via* the arc evaporation of graphite (Govindaraj and Rao, 2002). Soon after, this breakthrough, CNTs were obtained as an end product of ethylene and/or acetylene pyrolysis over iron (Fe) and cobalt (Co), etc. (Iijima, 1991; Teng et al., 2010; Ivanov et al., 1994; Faraji and Wipf, 2009). The presences of metals significantly influenced CNTs size profile (Sen et al., 1997). MWCNTs were synthesized by the pyrolysis of metallocenes (ferrocene, cobaltocene, and nickelocene) under reducing conditions; metallocene acted both as a carbon and metal source (Jang and Yoon, 2003). Pyrolysis of nickelocene at 1100 °C in benzene produced MWCNTs. Replacing benzene with acetylene, while keeping the rest of conditions the same, primarily yielded SWCNTs. This change in size was attributed to the availability of a lesser number of carbon atoms per molecule (Iijima, 1991). Apart from the aforementioned techniques, SWNTs were also synthesized from the mixtures of dilute hydrocarbon-organometallic (Satishkumar et al., 1998; Suslick et al., 1996). Owing to the high aspect ratio, strength, electrical conductivity, electron affinity, and structure versatility, both CNTs and buckyballs have shaped prospective academic and commercial interests (Bruchez

Table 2 Global production of nanostructure materials (Royal Society and Royal Academy of Engineering, 2004).

Application	Nanomaterial device	Estimated global production (tons/year)		
		2003/04	2010	2020
Structural application	Ceramics, catalysts, film & coating, composites, metal	10	10^3	10^4–10^5
Sink care products	Metal oxides (e.g., TiO_2 and ZnO)	10^3	10^3	10^3
Information and communication technologies	SWCNT, nanoelectronics and optoelectronics materials (excluding CMP slurries), organic light emitters	10	10^2	$>10^3$
Biotechnology	Nanocomposite, encapsulates, target drug delivery, diagnostic marker, biosensors	<1	1	10
Environmental	Nanofiltration membranes	10	10^2	10^3–10^4

et al., 1998). Metals (Au, Ag, etc.) and metal oxides (ZnO, TiO_2, SiO_2, Fe_3O_4, etc.) and metal composites (QDs), are the inorganic functional materials with exceptional optical, electrical and magnetic properties (Frens, 1973; Ullman, 1996). Au NPs are frequently synthesized *via* the chemical reduction of Au salts in aqueous, organic, or mixed solvent systems in the presence of stabilizers (citrate (http://www.bccresearch.com/editors/RGB-290.html; accessed July 03, 2011) and thiol-containing organic groups (Medintz et al., 2005). In the process stabilizers attach to the surface and prevent aggregation *via* favorable cross-linking and charge properties), micro-emulsions (Suslick et al., 1996), polymer coatings (Moyer, 1965), etc. Ag existed even before Neolithic revolution; Greeks used Ag for keeping the drinking water safe and for cooking (Wang et al., 2005). A variety of techniques have been employed to synthesize Ag NPs, these include Ag ions chemical reduction in aqueous (Project on Emerging Nanotechnologies Consumer Products Inventory, 2008; Pileni et al., 1993; Suslick et al., 1996; Leopold and Lendl, 2003; Caswell et al., 2003; Pillai and Kamat, 2004; Yin et al., 2002; Zhu et al., 2004) or non-aqueous solutions (Chaki et al., 2004; Sun et al., 2003; Sun and Xia, 2002), template method (Chen and Huang, 2002; Wang et al., 2003; Faure et al., 2003; Chen and Carroll, 2002; Mandal et al., 2003; Malandrino et al., 2004), electrochemical/ultrasonic-assisted reduction (Malandrino et al., 2004; Behrens et al., 2004; Morley et al., 2002; Johans et al., 2002; Zhang et al., 2002), photo-induced reduction (Ma et al., 2004; Yin et al., 2003; Cheng and Yao, 2005; Socol et al., 2002; Shchukin et al., 2003; Zhang et al., 2003a; Junior et al., 2003; Jin et al., 2003), microwave-assisted synthesis (Mallick et al., 2004; Kryukov et al., 2003; Cozzoli et al., 2004; Liu et al., 2004; Yamamoto et al., 2004; Komarneni et al., 2002), irradiation reduction (Yin et al., 2004; Qin et al., 2002; Hornebecq et al., 2003; Choi et al., 2003), micro-emulsion (Xin et al., 2004; Tsuji et al., 2003; Zheng et al., 2004; Zheng et al., 2003; Zhang et al., 2003b; Maillard et al., 2003; Maillard et al., 2002), biochemical reduction (McLeod et al., 2003; Egorova and Revina, 2002; Naik et al., 2002; Gardea-Torresdey et al., 2003; Shankar et al., 2003; Kowshik et al., 2003), etc. Ag NPs have found their application in drug determination techniques as sensor. TiO_2 NPs are the other valuable and mostly used NPs, which are prepared *via* low-pressure spray pyrolysis (LPSP) of organic precursors (Kim and Kim, 2002), hydrolysis and condensation of titanium tetra ethoxide (TEOT), vaporized water using a continuous aging tube reactor (Mahshid et al., 2007), hydrolysis of titanium isopropoxide (Dreesen et al., 2009), reactive direct-current magnetron sputtering (Figgemeier et al., 2007), laser pyrolysis of titanium tetrachloride-based gas-phase mixtures (Prasad et al., 2010), modified sol–gel technique, etc. (Jang, 2001). SiO_2 was synthesized by the oxidation of tetraethylorthosilicate (TEOS) in the bench-scale diffusion flame rector (Corradi et al., 2006), hydrolysis and condensation of TEOS using continuous microwave process (Rao et al., 2005), two-stage hydrolysis of silicon powder in aqueous medium (Chang et al., 2008), ultrasonic sol–gel process (Gupta and Gupta, 2005), flame pyrolysis, etc. (Guin and Manorama, 2008). Quite a few iron-based oxides, alloy, heterodimers and core shell materials not only exist in nature but could also be efficiently synthesized in various size. One of the most economic and environment-friendly method is co-precipitation. This method involves the co-precipitation of Fe^{2+} and Fe^{3+} ions in strong basic aqueous media. Beside co-precipitation, these could be also synthesized *via* in situ approach at room temperature in the presence of modifier. Highly dispersible α-Fe_2O_3 NPs were synthesized in the presence of oleic acid/toluene mixture at atmospheric pressure, low temperature, and at an ultra-dense reagent concentration using basic media (e.g., aqueous ammonia solution) (Iijima et al., 2008). Iron-based nanostructures (Fig. 2I) due to their better biocompatibility compared to other magnetic oxides or pure metals are frequently used in biomedical investigation (Fig. 2II) (Iijima et al., 2008).

QDs are metalloids e.g., CdSe/ ZnS in which the crystalline CdSe is the core and ZnS is the shell. The core is usually composed of a noble transition metal or semiconductor metal complex whereas the shell is formed during synthesis. The shell as discussed shields the core by making a hydrophobic layer around the core hence reduces QDs use in biological fields. To utilize QDs in biological fields these need to be biocompatible. Therefore, these are usually coated with hydrophilic materials, which improve the water wetting ability/solubility of QDs. Due to the quantum constraints imposed on electrons by the finite size, QDs display a fine fluorescence band (Wiesner and Bettero, 2007), which, make them optimal fluorophores for in vivo biomedical imaging (Aillon et al., 2009; Alivisatos, 2004). Fluorescent QDs with bioactive moieties (e.g., antibodies, receptor ligands) were not only used for the labeling of neoplastic cells, peroxisomes, deoxyribonucleic acid (DNA), and cell membrane receptors, but could also be used as target specific delivery device that could deliver gene and drugs to site-specific targets. Beside biomedical applications, QDs have also been used in the manufacturing of advance light-emitting diode (LED) and ultrahigh-density data

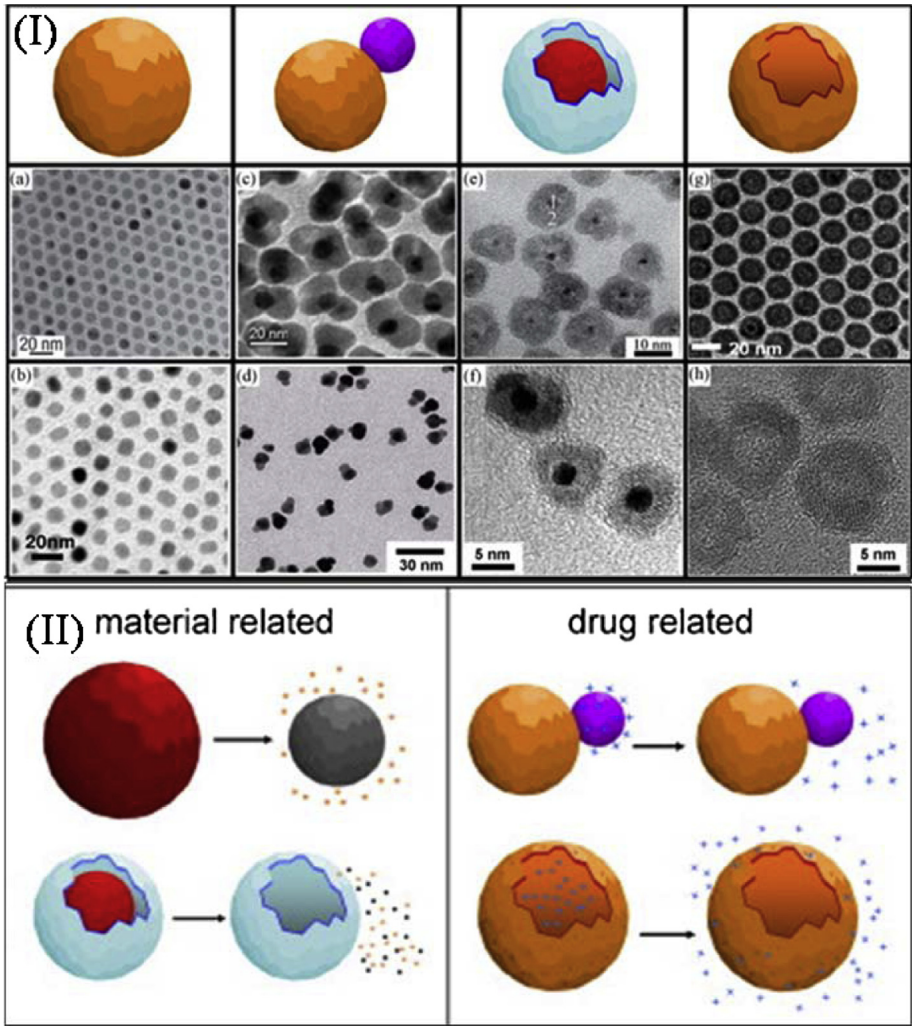

Figure 2 (I) Schematics of iron-based nanostructures (a) Fe_3O_4 NPs,(b) FePt alloy,(c) Fe_3O_4–Au heterodimers, (d) or FePt–Au, (e) yolk–shell nanostructures with FePt core and CoS_2 shell, (f) or Pt–Fe_2O_3,(g) Fe_3O_4 and/or (h) Fe_2O_3 hollow nanocrystals. (II) Different approaches for achieving therapeutic effect using NPs. In the first instance, degradation of the FePt NPs releases iron ions or iron and platinum ions simultaneously (partial (top left) or complete (lower left,) whereas in the second instance, NPs are loaded with cisplatin either by grafting the drug onto the surface of the Au domain in Au–Fe_3O_4 dumbbells (top right) or by embedding the drug in the inner regions of the hollow Fe_3O_4 NP (lower right). All reported systems are responsive to the decrease of the pH. The drug was released in the controlled manner (Figuerola et al., 2010).

storage and quantum information processing (Hardman, 2006).

1.2. Nanostructures and characterization techniques

Biological properties of nanostructures are sensitive to both physical characteristics (such as size, shape, surface area to volume ratio, agglomeration, dissolution rate, etc.) and chemical composition of the nanostructure surface. These could impart unique mechanisms of toxicity to nanostructures (Lanone and Boczkowski, 2006). Surface composition in particular determines the nature of chemical interactions of nanostructures with the target whereas the limited bulk volume is hidden (Powers et al., 2006). It is therefore essential for nanostructures to be compatible to a particular system. This could be done by proper surface functionalization e.g., in biological use nanostructures could be functionalized to alter their biological functions, improve their biocompatibility, interactivity with biological materials, breaking into cells, etc. Non-degradable nanostructures gather in organs and in intra-cellular vicinity and cause detrimental effects (e.g., lysosomal storage diseases) to the cell (Garnett and Kallinteri, 2006). Biodegradable nanostructures containing transition metals, on the other hand could discharge toxins to the biological environment. These toxins might generate highly unstable species (free radicals), which would result in cellular damage (Lanone and Boczkowski, 2006; Fischer and Chan, 2007). Another major cause of nanostructure toxicity is their aggregation. Aggregation arises from size, intrinsic high dispersion and surface energy, and affects colloidal stability, homogeneity, cell or bacterial uptake/targeting, etc. It is therefore critical to perform sizing and aggregation stability assays of the nanostructures in biological solution, before studying their colloidal stability, homogeneity, cell or bacterial uptake/targeting, etc. The methods used more

recently for the determination of particle sizes and their aggregation are; direct imaging techniques (Transmission Electron Microscopy (TEM), Scanning Electron Microscopy (SEM), Atomic Force microscopy (AFM), etc.), spectroscopic techniques (Energy Dispersive X-ray Spectroscopy (EDS), Optical Spectroscopy, Ultra violet and visible (UV–vis) Spectroscopy, X-ray absorption spectroscopy, Surface Plasmon Resonance (SPR), etc.), fluorescent techniques (Time-Resolved Fluorescence Polarization Anisotropy (TRFPA)), light scattering technique (Dynamic Light Scattering (DLS)), etc. However, these methods have their limitations and do not often come with significant results in complex systems. These could only produce best results either in pre-experimental characterization or when corroborated with other techniques. TEM is a conventional direct electron imaging technique used to study morphology, shape, size distribution and aggregation of non-metallic (Fig. 3d–e) and metallic nanostructures (Fig. 3f–h) (Tian et al., 2006; Soto et al., 2007; Jones and Grainger, 2009; Davoren et al., 2007; Wilson et al., 2002; Geiser et al., 2005), though in the former case Emission Field Transmission Electron Microscope (EFTEM) was used due to the energy filtering variation. However, having said this ex-situ particle aggregation information provided by TEM does not essentially represent the in situ aggregation states. The main cause for this limitation is the sample artifacts, produced in the sample during its preparation. To avoid the formation of artifacts, flash freezing and desiccation techniques could be used during sample preparation. This is quite tiresome and needs a lot of practice. For this very reason, TEM should be corroborated by other methods, e.g., zeta-potential, gel electrophoresis, etc. (Jones and Grainger, 2009). Sometimes, TEM are also equipped with EDS for obtaining elemental analysis, X-ray absorption spectroscopy for determining three dimensional structures and AFM for measuring particle surface morphology in three dimensions. Despite its limitations, TEM is widely used and still considered a potent apparatus to discriminate between crystalline , amorphous particulate and aggregation (e.g., distinguishes fullerene aggregate from fullerene crystalline in resin-fixed and freeze-dried cells) (Jones and Grainger, 2009; Davoren et al., 2007; Wilson et al., 2002; Geiser et al., 2005; Soto et al., 2006). SEM is another potent technique, mainly used for studying the surface features of materials; beside this it has also been used for particles sizing and aggregation studies. Traditional SEM requires ultra-high vacuum conditions (UHV) and dried samples (Fig. 3a–c) (Jones and Grainger, 2009) and has its limitation in getting accurate data in situ. This problem has been solved and more recently the liquid (water) surface and objects in the vicinity of liquid surface could be imaged under the same UHV conditions using Emission Scanning Electron Microscopy (ESEM). Furthermore, a modification in the standard ESEM protocols (to utilize a Peltier element (to control evaporation)) and transmission mode

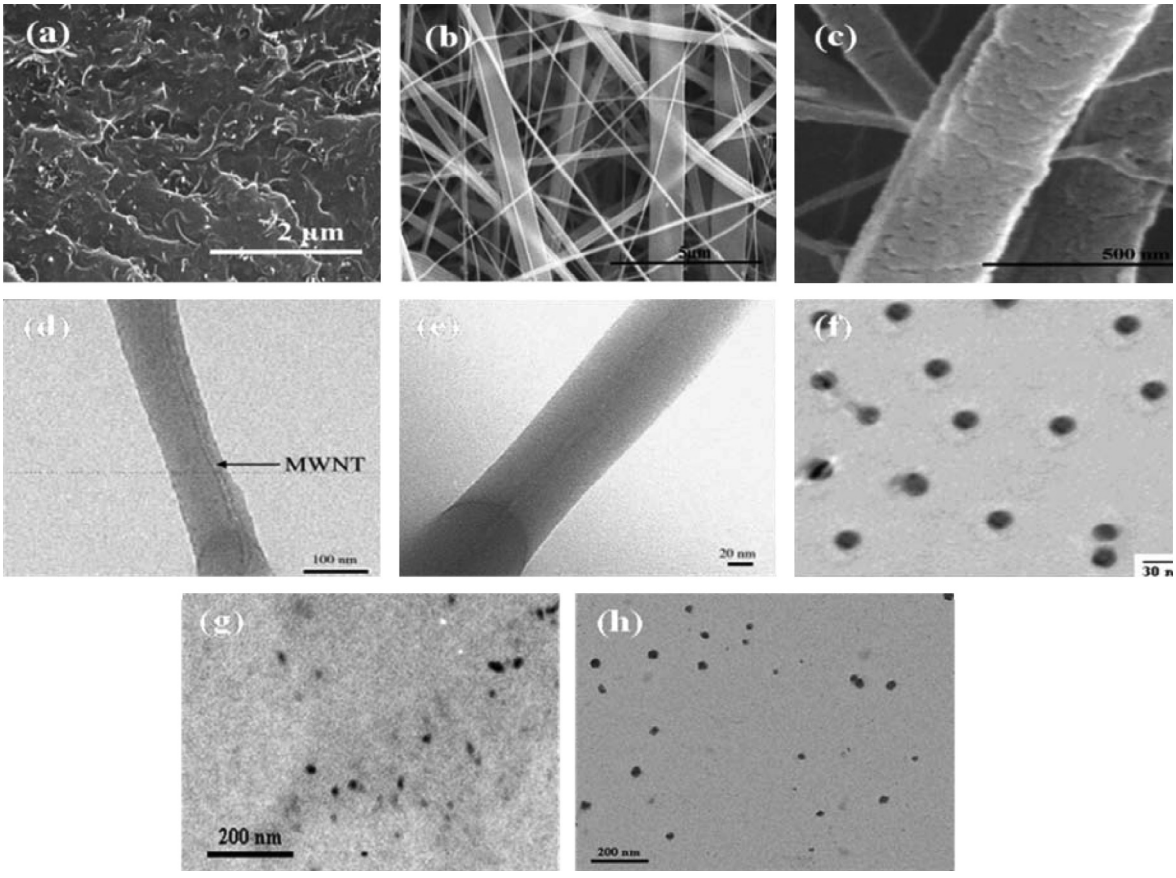

Figure 3 SEM micrographs of (a) MWCNTs, (b) chitosan nanofibers, (c) freeze-dried chitosan nanofibers, (d) and (e) TEM micrographs of f-MWCNTs/caprolactone composite nanofibers, (f) Ag NPs, (g) magnetic NPs coated with oleic acid and (h) maleic anhydride-co-β-cyclodextrin coated magnetic NPs (Haider et al., 2007; Haider and Park, 2009; Saeed et al., 2006; Alothman et al., 2010; Omer et al., 2011).

of the instrument (wet scanning transmission electron microscopy (STEM)) expanded the abilities of ESEM to micro-image emulsions and particle suspensions (Bogner et al., 2005).

SPR optical effects are shape, diameter, surface adsorbates and inter plasmonic particles distance dependent. Metals and metal NPs show size-dependent absorption and scattering of light through excitation of the metal's plasmon band electrons. Binding of adsorbate to metal could modify the surface interband electronic states, which could result in the change of surface plasmon band extinction. Au/Ag NPs are frequently sized by measuring their extinction wavelength (Jones and Grainger, 2009). As the average diameter of metal NPs increases, the plasmon peak shifts from red to higher optical and extinction wavelengths. The shift in the absorption and extinction wavelengths differentiates between clean and ligand adsorbed NPs (e.g., contaminants, stabilizing layers, proteins, DNA, etc.) (El-Sayed, 2004). On the contrary a shift in absorbance from red to blue color, when the inter-NP distance is smaller than average NP diameter, could be used as a particle aggregation indicator, e.g., a shift from red to blue color for Au colloidal solution indicates aggregation. However, this technique has its limitation for application in biological environment, because in such an environment non-specific adsorption induces particle aggregation; therefore it is difficult to distinguish the effects of particle surface adsorption and the resulting aggregation. DLS is used extensively for the measurement of NPs hydrodynamic size in solution, aggregation (Fig. 4a and b) and polydispersity studies (Omer et al., 2011; Lin et al., 2006). However, NPs sizing analyses by DLS need a high level of expertise in calibrating the instrument, understanding positive and negative controls, purities and optical data modeling algorithms for predicting size distribution. A large number of particle size distribution studies (for spanning metals, metal oxides and polymers) use this technique blindly as an automated method with default scattering models and curve fitting assumptions; that are neither described, justified or validated. Unwanted adsorbates and solutes in NP systems could be removed *via* dialysis or centrifugation and aggregates could be broken up in sonication bath (Tian et al., 2006). However, care must be taken during sonication (bath or probe) since it is hard to standardize their density, dose, power, local heating, etc. These parameters every so often have unnecessary effects on the sample, e.g., the shedding of metal particles from the probe tip and oxidation of surface active sites. (Castner, 2008). Theoretically DLS is better applied in micro-scale size regimes in which particles scatter much more light compared to nano-size regimes. The presence of small amounts of contaminants easily tilt DLS data; beside this NP solutions are very sensitive to small changes in salt (increasing salt concentration decreases colloid stability) and protein (charge stabilized particles aggregate rapidly in the presence of protein (oppositely charged)) (Jones and Grainger, 2009).

Therefore, it is essential to design DLS studies of NPs carefully. Sample calibration could be carried out with sizing standards appropriate to the experiment. A number of standards are accessible, which could aid researchers; these are; American society for testing and materials (ASTM) standard for determination of NP size distribution in suspension using photon correlation spectroscopy (ASTM E2490-08) and the national institute of standards and technology (NIST), "gold standard" (NIST RM8011, NIST RM8012 and NIST RM8013), etc. In case of the biological environment (which is sensitive to ionic strength, polymer, surfactant, peptide, proteins, etc.), researchers are hunting for more precise techniques, which would enable them to acquire highly reproducible data. TRFPA could determine the NP size from 1 to 10 with 0.1 nm resolutions by correlating fluorescence polarization decay time to fluor or particle size (hydrodynamic radius). TRFPA utilizes sub-nanosecond-resolution laser pulses and detectors to excite fluors in assay environment. The decay of fluorescence polarization distinguishes particle or fluor binding to receptors from assay components. TRFPA has the potential to track the pathways of toxicity by relating labeled NPs fluorescence anisotropy to NPs-cell receptor interactions and by correlation with toxicity endpoints (Jones and Grainger, 2009). So far this method has not found ample application in nano size distribution assays. Besides the above techniques, large angle X-ray diffraction (XRD) (Omer et al., 2011; Castner, 2008), multi-angle laser light scattering (MALLS) in combination with UV–vis spectroscopy, small angle X-ray

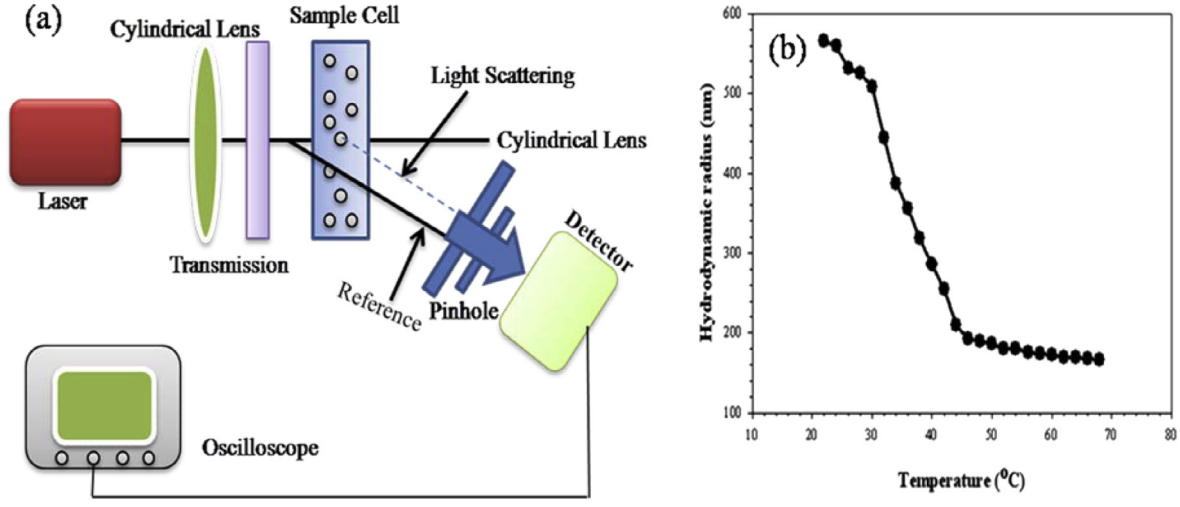

Figure 4 (a) Schematic of DLS setup and (b) hydrodynamic radii measurement of poly (NIPAAm)–MNPs in aqueous medium (Omer et al., 2011).

scattering (SAXS) and small angle neutron scattering (SANS) have also been used for regularly sizing nanostructures.

2. Nanostructures as a potential toxic hazard

With numerous nano products already in the market, the debate on their potential threats and societal implications has gained moment. A worldwide 1.5–2 million human deaths per annum attributed mostly to indoor nano-particulate air pollution show the severity of the problem. A careful review of nanotoxicity will not only aid in determining environmental and health risks of the marketed nanostructures but will also facilitate industry to develop safer nano-products. These measures will help improve the public trust of the nanotechnology industry (Hoet et al., 2004; Usenko et al., 2007). The unexplored risks associated with nanostructures, as discussed in the previous section, lead to complication when used in biological system. Hence it is imperative to take into account nanostructures' agglomeration (coagulation and coalescence), sedimentation and diffusion at relevant physiological concentrations while performing their quantitative studies in biological systems. Additionally, it is also essential, to evaluate the risk posed by nanostructures to ecology and conclude their environmental gravity. In the ecosystem the fate of nanostructures is controlled by solubility/dispersability, agglomeration (coagulation and coalescence), natural/anthropogenic chemicals, etc. Alumina (Al_2O_3), TiO_2 and ZnO NPs are commonly used in the preparation of the UV protection products such as scratch-resistant transparent coatings and sunscreen lotions. Among these Al_2O_3 have been observed to retard the root growth of the corn, cucumber, soybean, cabbage and carrot (phytotoxicity). At present only TiO_2 NP based sunscreen filters are the only authorized (on the European Union directive on cosmetics list of permitted UV filter) sunscreen filters (Salvador and Chisvert, 2005). Fullerene-$C_{60,}$ affects the ecosystem by elevating lipid peroxidation (LPO) in aquatic species (Daphnia and Pimephales) and gene expression associated to inflammatory response and metabolism in CYP2 family.

Having discussed NPs toxicity, it must be right to say that all NPs are not hazardous. The toxicity assay of SiO_2 NPs carried out on mice (used as model) showed that SiO_2 NPs are harmless and could be used in vivo. Furthermore, the environmental risks associated with the manufacturing of SWCNTs, C_{60}, QDs, alumoxane (Al_2O_3 based particles, analogous to poly-siloxanes) and TiO_2 NPs were reasonably low as compared to those common industrial manufacturing processes. However prolonged exposure to these materials may cause chronic toxicity. Today, the need has aroused to categorize regimes to protect human resource involved in the manufacturing and utilization of NPs for cosmetic, medical and agricultural purposes (Royal Society and Royal Academy of Engineering, 2004). However, this should not be the end of search for ecologists, further work is needed to draw conclusion about the toxicity threshold and determine whether or not a particular NP has toxic effect to ecology. Cytotoxicity associated NPs exposure is somewhat particle specific (Table 3) some cases are discussed in the below sections (Wiesner et al., 2006; Braydich-Stolle et al., 2005).

2.1. In vitro assessment of nanostructures toxicity

The toxicity of carbonaceous NPs has been widely studied and numerous cellular interaction/cytotoxicity mechanisms (Fig. 5) for SWCNTs and MWNCTs are reported in the literature. SWCNTs containing iron traces (unrefined) exerted oxidative stress and caused cellular toxicity in human epidermal keratinocytes in the concentration range of 0.6–0.24 g mL^{-1} and exposure of 2–8 h (Shvedova et al., 2003) and purified SWCNTs inhibited cell reproduction and decreased cell adhesability in human embryo kidney cells (HEK293) in the concentration range of 0.8–200 μg mL^{-1} (Cui et al., 2005), whereas functionalized SWCNTs caused cytotoxicity in the

Table 3 Toxicity of some selected nanostructures (Wiesner et al., 2006).

Nanomaterial	Toxicity
Fullerene C_{60} water suspension	Antibacterial; cytotoxic to human cell lines; taken up by human keratinocytes; stabilizes proteins
C_{60} encapsulation in poly(vinyl-pyrrolidone), cyclodextrin, or poly(ethylene glycol)	Damages eukaryotic cell lines; antibacterial
Hydroxylated fullerene	Oxidative eukaryotic cell damage
Carboxyfullerene (malonic acid derivatives)	Bactericidal for gram-positive bacteria; cytotoxic to human cell lines
Fullerene derivatives with pyrrolidine groups	Antibacterial; inhibits cancer cell proliferation; cleaves plasmid DNA
Other alkane derivatives of C_{60}	Anti mutagenic; cytotoxic; induces DNA damage in plasmids; inhibits protein folding; antibacterial; accumulates in rat livers
Metallofullerene	Accumulates in rat livers
Silicon dioxide (SiO_2)	Pulmonary inflammation in rats
Titanium dioxide (TiO_2) (Anatase)	Antibacterial; pulmonary inflammation in rodents
Zinc oxide (ZnO)	Antibacterial (micrometer scale); pulmonary effects in animals and humans
Silver (Ag)	Most toxic to spermatogonial stem cell line in the male germ line
Molybdenum trioxide (MoO_3)	Least toxic to spermatogonial stem cell line in the male germ line

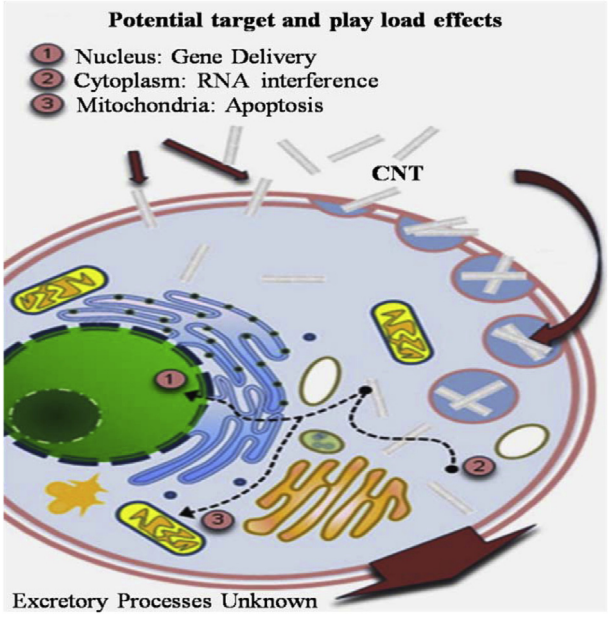

Figure 5 Schematic shows two mechanisms for nanomaterial interactions with cell; (1) endocytosis/phagocytosis and (2) nanopenetration. Endocytosis is the engulfing of extracellular particles of 100 nm in size through the creation of a vesicle. The vesicle is then included into the cell. Phagocytosis is analogous to endocytosis; however, involves large particles (such as bacteria (1 μm) uptake and is characteristic to a subset of immune cells/phagocytes (e.g., neutrophils, macrophages, dendritic cells) (Firme and Bandaru, 2010).

human dermal fibroblasts (Lewinski et al., 2008). Furthermore, SWCNTs with a trace amount of metal catalysts (other than iron) showed a more toxic response to alveolar macrophages isolated from guinea pigs compared to MWCNTs, quartz and fullerene and could prove to be a potential occupational health hazard when inhaled (Davoren et al., 2007). Pristine MWCNTs in the concentration of 0.1, 0.2, and 0.4 mg mL^{-1} and exposure of 1–48 h, decreased the viability of human osteoblastic lines and human epidermal keratinocytes. MWCNTs after oxidation were observed to be more cytotoxic toward Jurkat T leukemia cells (Monteiro-Riviere and Inman, 2006). The results of the cytotoxicity studies carried out in the bacterial system using pristine and physicochemical modified MWCNTs (i.e., decapped, exfoliated, small, and highly dispersed in solvent) showed maximum toxicity in the latter case. These results concluded that the physicochemical characteristics are vital in toxicity caused by CNTs. Hence it is imperative to take into account the physicochemical characteristics of CNTs while documenting their toxicity.

Contrasting reports about the toxicity caused by fullerenes (C_{60}) are available/documented in the literature, e.g., in one report the viability of bovine and human alveolar macrophages reduced and the levels of cytokine mediators of inflammation (i.e., IL-6, IL-8 and TNF) increased when exposed to sonicated C_{60}, while in another, no toxicity of C_{60} and raw soot was found. This inconsistency between the two results could be attributed to the two different analyzing techniques e.g., in the former case viability assay based on metabolic activity was used while in the latter TEM was used to micro-image the distributions of C_{60} within the macrophages. Furthermore dose-dependent cytotoxicity of C_{60}(OH) and C_{60}-phenylalanine resulted in the decrease of cell density and lactate dehydrogenase (LDH) release in human umbilical vein endothelial cell cavity and cell viability of human epidermal keratinocytes (no contribution was attributed to phenylalanine group). The toxicity caused by QDs is mainly affected by its composition, size, surface charge and outer surface coating. Cadmium selenide (CdSe)/zinc sulfide (ZnS) QDs coated with dihydrolipoic acid (DHLA) showed toxicity to mammalian cells, whereas CdSe/ZnS QDs coated with albumin showed adverse effects on mouse lymphocytes. QDs also showed size, light and temperature dependent cytotoxicity e.g., under the same conditions, positively charged small (i.e., 2.2 ± 0.1 nm) QDs exhibited stronger cytotoxicity compared to large (i.e., 5.2 ± 0.1 nm) ones. The exposure of DNA to CdSe/ZnS in the presence of ultraviolet (UV) light caused 56% damage to DNA compared to the 29% in the absence of UV light. Similarly CdSe/cadmium sulfide (CdS) showed toxicity to cancer cells at 37 °C, whereas at 4 °C no toxicity was observed at all. Metal NPs such as Ag is an effective bactericide against S.epidermidis; it effectively kills E. coli bacteria too. Whereas exposure of immortalized rat lung epithelial cells to 520 μg cm^{-2} Zn NPs for 1 h increased the production of LDH levels (an indicator of inflammation). Metal oxide NPs such as Anatase TiO_2, SiO_2, and coated Fe_3O_4 killed human dermal fibroblast (HDF) cells at a lethal concentration (LC_{50}) of 3.6 μg mL^{-1}, decreased the viability of human lymphoblastoid cells (at the concentration of 0–130 μg mL^{-1} and exposure time of 6–48 h), significantly inhibited replication and transcription in human epithelial HEp-2 cells (at the concentration of 25 μg mL^{-1} exposure time of 24 h), and decreased the viability of human monocyte macrophages, respectively (Hristozov and Malsch, 2009).

2.2. In vivo assessment of nanostructures toxicity

Nanostructures have shown dose, size and functional group dependent in vivo toxicity. The carbonaceous nanostructures such as SWCNTs have shown interstitial inflammation and lesions in mice and rats at the concentration of 0–0.5 mg·kg^{-1} and exposure of 7 to 90 days (Lam et al., 2006). SWCNT soot was also found to cause pulmonary granulomas in rats at concentration of 1 and 5 mg·kg^{-1} and exposure of 24 h to 3 months. The first study was dose dependent whereas the latter was dose independent. The eco-toxicity study carried out on a rainbow trout exposed to SWCNTs (sonicated in the concentrations of 0.1, 0.25 and 0.5 mg L^{-1} with surfactant (sodium dodecyl sulfate (SDS)) for 24 h to 10 days showed not only a dose-dependent increase in ventilation rate, gill pathologies (edema, altered mucocytes, hyperplasia), and SWCNT precipitated mucus secretion but also substantially decreased thiobarbituric acid reactive substances (TBARS) in gill, brain and liver (Hristozov and Malsch, 2009; Smith et al., 2007; Warheit et al., 2004). On the other hand MWCNTs showed size and morphology dependent acute toxicity in rats with the lethal dose (LD_{90}) of 5 mg·kg^{-1} (e.g., lengthy MWCNTs caused substantial inflammation and tissue damage in mice compared to shorter MWCNTs). Furthermore MWCNTs soluble in aqueous medium did not show strong inflammatory effects in mice. Functionalized C_{60} e.g., hydroxylated C_{60} (C_{60}(OH)) caused acute oxidative stress in living organisms e.g.,

substantial increase in lipid peroxidation (LP) was observed when C_{60} (OH) at the concentration of 1 mg kg^{-1} was administrated intravenously in male mongrel dog. Likewise, high LP was also found in the brain and gills of daphnia magna on exposure to C_{60} (OH) and in tetrahydrofuran (THF) dispersed C_{60} (no contribution of THF was observed). Metal and metal oxide NPs provoke harsh lung toxicity in mice compared to bulk materials of the same type (Li et al., 1999). Zn NPs showed toxicity to humans at higher concentration (e.g., the exposure to a concentration of 5 mg m^{-3} Zn NPs for 2 h, causes sore throat, chest tightness, headache, fever, chills, etc.) whereas at low concentration (i.e., 500 μg m^{-3}) no such effect was observed. Zn NPs were also observed to cause lethargy, anorexia, vomiting, diarrhea, loss of body weight and even death in mice when administered gastro intestinally whereas a decreased effect was noted for micro-scale Zn at equal concentrations. Al NP administration of 2 mg mL^{-1} for 24 h inhibited the growth of Zea mays (corn), glycine max (soybean), Brassica oleracea (cabbage), and Daucus carota (carrot). Metal oxide NPs such as TiO_2 and SiO_2 also caused size dependent toxicity (e.g., smaller TiO_2 and SiO_2 NPs caused severe pulmonary damage in mice and severe lung inflammation in rats, respectively) compared to their larger counterparts. Administration of a single-dose intravenous bolus of NPs at concentrations of 20 and 200 mg kg^{-1} caused hypoactivity, ataxia, emesis, exophthalmos, salivation, lacrimation, discolored and mucoid feces, injected sclera, and yellow eyes in dogs and a substantial increase in fetal skeletal malformations in rats and rabbits (Hristozov and Malsch, 2009).

3. Conclusion

Investment in nanotechnology is on the rise and a variety of engineered nanostructures and processes has emerged. Despite the increased investment and improved knowledge in the design and synthesis of nanostructure materials, an in-depth knowledge of their size, shape, composition and aggregation dependent interactions with humans, animals, insects and plants are still foggy. Beside, this, the characterization methods need be to carefully calibrated and used. The toxicity testing protocols should be made more specific as it is not wise to generalize it for all NPs. At the present rate of research and development in nanotechnology, we may require quite a few years to understand the health and environmental risks and then form an environmentally safe protocol to protect human resource involved in the manufacturing and use of NPs. To achieve this goal a comprehensive and collaborated strategy between industrialists, government, toxicologists and material scientists will be very helpful.

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